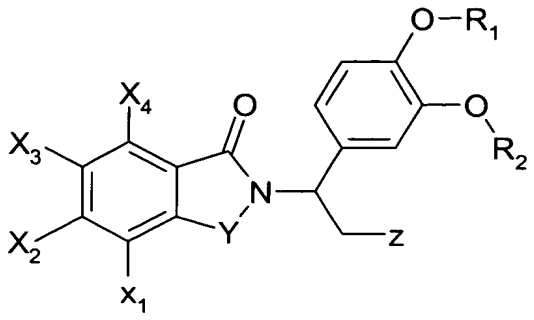
WHAT IS CLAIMED IS:

1. A compound having the formula (**I**):



I

wherein:

Y is -C(O)-, -CH_2, -$CH_2C(O)$-, -$C(O)CH_2$-, or SO_2;

Z is –H, -$C(O)R^3$, -(C_{0-1}-alkyl)-SO_2-(C_{1-4}-alkyl), -C_{1-8}-alkyl, -CH_2OH, $CH_2(O)$(C_{1-8}-alkyl) or -CN;

R_1 and R_2 are each independently -CHF_2, -C_{1-8}-alkyl, -C_{3-18}-cycloalkyl, or -(C_{1-10}-alkyl)(C_{3-18}-cycloalkyl), and at least one of R_1 and R_2 is CHF_2;

R^3 is -NR^4R^5, -alkyl, -OH, –O-alkyl, phenyl, benzyl, substituted phenyl, or substituted benzyl;

R^4 and R^5 are each independently –H, -C_{1-8}-alkyl, -OH, -$OC(O)R^6$;

R^6 is –C_{1-8}-alkyl, -amino(C_{1-8}-alkyl), -phenyl, -benzyl, or -aryl;

X_1, X_2, X_3, and X_4 are each independent -H, -halogen, -nitro, -NH_2, -CF_3, -C_{1-6}-alkyl, -(C_{0-4}-alkyl)-(C_{3-6}-cycloalkyl), (C_{0-4}-alkyl)-NR^7R^8, (C_{0-4}-alkyl)-$N(H)C(O)$-(R^8), (C_{0-4}-alkyl)-$N(H)C(O)N(R^7R^8)$, (C_{0-4}-alkyl)-$N(H)C(O)O(R^7R^8)$, (C_{0-4}-alkyl)-OR^8, (C_{0-4}-alkyl)-imidazolyl, (C_{0-4}-alkyl)-pyrrolyl, (C_{0-4}-alkyl)-oxadiazolyl, or (C_{0-4}-alkyl)-triazolyl or X1 and X2 or X2 and X3 or X3 and X4 are taken together with the atoms that join them to form a cycloalkyl or heterocycloalkyl ring of 3, 4, 5, 6 or 7 atoms; and

R^7 and R^8 are each independently H, C_{1-9}-alkyl, C_{3-6}-cycloalkyl, (C_{1-6}-alkyl)-(C_{3-6}-cycloalkyl), (C_{1-6}-alkyl)-$N(R^7R^8)$, (C_{1-6}-alkyl)-OR^8, phenyl, benzyl, or

aryl; or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

2. The compound of Claim 1 wherein, one of X_1, X_2, X_3, and X_4 is (C_{0-4}-alkyl)-NR^7R^8.

3. The compound of Claim 1 wherein, one of X_1, X_2, X_3, and X_4 is (C_{0-4}-alkyl)-$NHC(O)(R^8)$.

4. The compound of Claim 1 wherein, one of X_1, X_2, X_3, and X_4 is (C_{0-4}-alkyl)-$NHC(O)(R^8)$ and one of X_1, X_2, X_3, and X_4 is halogen.

5. The compound of Claim 1 wherein one of X_1, X_2, X_3, and X_4 is (C_{0-4}-alkyl)-$NHC(O)NR^7R^8$.

6. The compound of Claim 1 wherein, one of X_1, X_2, X_3, and X_4 is (C_{0-4}-alkyl)-$NHC(O)O(R^7R^8)$.

7. The compound of Claim 1 wherein, one of X_1, X_2, X_3, and X_4 is (C_{0-4}-alkyl)-OR^8.

8. The compound of Claim 1 wherein, one of X_1, X_2, X_3, and X_4 is (C_{0-4}-alkyl)-imidazolyl, (C_{0-4}-alkyl)-pyrrolyl, (C_{0-4}-alkyl)-oxadiazolyl, or (C_{0-4}-alkyl)-triazolyl.

9. The compound of Claim 1 wherein, one of X_1, X_2, X_3, and X_4 is (C_{0-4}-alkyl)-cyclopropyl.

10. The compound of Claim 1 wherein, one of X_1, X_2, X_3, and X_4 is NH_2.

11. The compound of Claim 1 wherein, three of X_1, X_2, X_3, and X_4 are H.

12. The compound of Claim 1 wherein X_1 and X_2 are H or X_3 and X_4 are H.

13. An enantiomerically pure S isomer of a compound of claim 1, substantially free of its R isomer, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

14. An enantiomerically pure R isomer of a compound of claim 1, substantially free of its S isomer, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

15. A compound selected from the group consisting of:

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-propionic acid;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-N,N-dimethyl-propionamide;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(3 cyclopropylmethoxy-4-difluoromethoxy-phenyl)-propionamide;

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid;

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-N-hydroxy-propionamide;

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-propionic acid methyl ester;

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-propionic acid;

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl -3-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-)-N,N-dimethyl-propionamide;

3-(7-Amino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-N,N-dimethyl-propionamide;

3-(4-Difluoromethoxy-3-ethoxy-phenyl)-3-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-propionic acid methyl ester;

3-(7-Amino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid methyl ester;

3-[7-(Cyclopropanecarbonyl-amino)-1-oxo-1,3-dihydro-isoindol-2-yl]-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid methyl ester;

3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid methyl ester;

3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid;

3-[7-(Cyclopropanecarbonyl-amino)-1-oxo-1,3-dihydro-isoindol-2-yl]-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid;

Cyclopropanecarboxylic acid {2-[2-carbamoyl-1-(4-difluoromethoxy-3-ethoxy-phenyl)-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

Cyclopropanecarboxylic acid {2-[1-(4-difluoromethoxy-3-ethoxy-phenyl)-2-dimethylcarbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-;

Cyclopropanecarboxylic acid {2-[1-(4-difluoromethoxy-3-ethoxy-phenyl)-2-hydroxycarbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionamide;

3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-N,N-dimethyl-propionamide;

3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-N-hydroxy-propionamide;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionamide;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-N,N-dimethyl-propionamide;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-N-hydroxy-propionamide;

Cyclopropanecarboxylic acid {2-[1-(4-difluoromethoxy-3-ethoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

N-{2-[1-(4-Difluoromethoxy-3-ethoxy-phenyl)-2-methanesulfonyl-ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl}-acetamide;

Cyclopropanecarboxylic acid {2-[2-carbamoyl-1-(4-difluoromethoxy-3-ethoxy-phenyl)-ethyl]-7-chloro-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

N-{2-[1-(4-Difluoromethoxy-3-ethoxy-phenyl)-3-morpholin-4-yl-3-oxo-propyl]-1,3-dioxo-2,3-dihydro-1H-isoindol- 4-yl}-acetamide;

N-{2-[1-(4-Difluoromethoxy-3-ethoxy-phenyl)-3-morpholin-4-yl-3-oxo-propyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-acetamide;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(3,4-bis-difluoromethoxy-phenyl)-N,N-dimethyl-propionamide;

3-(3,4-Bis-difluoromethoxy-phenyl)-3-[4-chloro-7-(cyclopropanecarbonyl-amino)-1-oxo-1,3-dihydro-isoindol-2-yl]-propionic acid methyl ester;

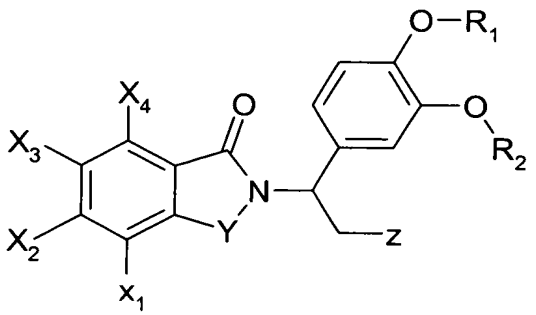
Cyclopropanecarboxylic acid {2-[1-(3,4-bis-difluoromethoxy-phenyl)-2-dimethylcarbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

Cyclopropanecarboxylic acid {2-[1-(3,4-bis-difluoromethoxy-phenyl)-2-carbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

Cyclopropanecarboxylic acid {2-[1-(3,4-bis-difluoromethoxy-phenyl)-2-hydroxycarbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide; and

3-(3,4-Bis-difluoromethoxy-phenyl)-3-[7-(cyclopropanecarbonyl-amino)-1-oxo-1,3-dihydro-isoindol-2-yl]-propionic acid.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, excipient, or diluent and a compound having the formula (**I**):



I

wherein:

Y is -C(O)-, -CH_2, -$CH_2C(O)$-, -$C(O)CH_2$-, or SO_2;

Z is –H, -$C(O)R^3$, -(C_{0-1}-alkyl)-SO_2-(C_{1-4}-alkyl), -C_{1-8}-alkyl, -CH_2OH, $CH_2(O)(C_{1-8}$-alkyl) or -CN;

R_1 and R_2 are each independently -CHF_2, -C_{1-8}-alkyl, -C_{3-18}-cycloalkyl, or -(C_{1-10}-alkyl)(C_{3-18}-cycloalkyl), and at least one of R_1 and R_2 is CHF_2;

R^3 is -NR^4R^5, -alkyl, -OH, –O-alkyl, phenyl, benzyl, substituted phenyl, or substituted benzyl;

R^4 and R^5 are each independently –H, -C_{1-8}-alkyl, -OH, -$OC(O)R^6$;

R^6 is –C_{1-8}-alkyl, -amino(C_{1-8}-alkyl), -phenyl, -benzyl, or -aryl;

X_1, X_2, X_3, and X_4 are each independent -H, -halogen, -nitro, -NH_2, -CF_3, -C_{1-6}-alkyl, -(C_{0-4}-alkyl)-(C_{3-6}-cycloalkyl), (C_{0-4}-alkyl)-NR^7R^8, (C_{0-4}-alkyl)-N(H)C(O)-(R^8), (C_{0-4}-alkyl)-N(H)C(O)N(R^7R^8), (C_{0-4}-alkyl)-N(H)C(O)O(R^7R^8), (C_{0-4}-alkyl)-OR^8, (C_{0-4}-alkyl)-imidazolyl, (C_{0-4}-alkyl)-pyrrolyl, (C_{0-4}-alkyl)-oxadiazolyl, or (C_{0-4}-alkyl)-triazolyl triazolyl or X_1 and X_2 or X_2 and X_3 or X_3 and X_4 are taken together with the atoms that join them to form a cycloalkyl or heterocycloalkyl ring of 3, 4, 5, 6 or 7 atoms; and

R^7 and R^8 are each independently H, C_{1-9}-alkyl, C_{3-6}-cycloalkyl, (C_{1-6}-alkyl)-(C_{3-6}-cycloalkyl), (C_{1-6}-alkyl)-N(R^7R^8), (C_{1-6}-alkyl)-OR^8, phenyl, benzyl, or aryl;

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

17. The pharmaceutical composition of claim 16 further comprising an additional therapeutic agent.

18. The pharmaceutical composition of claim 17 wherein the additional therapeutic agent is an anti-cancer agent, an anti-inflammatory agent.

19. The pharmaceutical composition of claim 18 wherein the anti-cancer agent is paclitaxel, cisplatin, tamoxifen, docetaxel, pirubicin, doxorubicin, irinotecan, leuprolide, bicalutamide, a goserlin implant, gemcitabine, sargramostim or steroids.

20. A method of inhibiting PDE4 in a mammal comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

21. A method of modulating the production of TNF-α in a mammal comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

22. A method of inhibiting matrix metalloproteinases in a mammal comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

23. A method of treating undesired angiogenesis in a mammal which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

24. A method of treating cancer in a mammal which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

25. The method of claim 24 wherein the cancer is a solid tumor or a blood-born tumor.

26. The method of claim 25 wherein the cancer is of the skin; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectal; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; or nasal passages.

27. A method of treating Myelodysplastic syndrome, myeloproliferative disease, complex regional pain syndrome, inflammatory disease, autoimmune disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, aphthous ulcers, cachexia, graft versus host disease, asthma, adult respiratory distress syndrome, acquired immune deficiency syndrome, inflammation of the lungs, depression, chronic obstructive pulmonary disorder, inflammatory bowel disease, atopic dermatitis, psoriasis, multiple sclerosis or heart disease in a mammal which comprises administering thereto an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

28. The method of claim 27 wherein the therapeutically or pharmaceutically effective amount of a compound of claim 1 is administered before, during or after surgery or physical therapy directed at reducing or avoiding a symptom of complex regional pain syndrome in the patient.

29. The method of any one of claims 20-24 wherein the effective amount of a compound of claim 1 is from about 0.1mg to about 300 mg per day.

30. The method of claim 29 wherein the effective amount is from about 1mg to about 250 mg per day.

31. The method of any one of claims 20-24 wherein the compound of claim 1 is administered orally, parenterally, topically or mucosally.

32. The method of any one of claims 20-22 wherein the mammal or mammalian cell is human.